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Original article

Glycaemic variability is associated with severity of coronary artery disease in patients with poorly controlled type 2 diabetes and acute myocardial infarction

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ABSTRACT

Background. – In patients with type 2 diabetes (T2D), glycaemic variability (GV), another component of glycaemic abnormalities, is a novel potentially aggravating factor for coronary artery disease (CAD).

Objectives: The aim of our study was to identify interactions between GV and severity of CAD in diabetes patients admitted for acute myocardial infarction (AMI).

Methods. – All patients with T2D admitted to our university hospital for AMI from March 2015 to February 2017 who received intravenous (IV) insulin therapy and underwent coronary angiography were included. GV was assessed by mean amplitude of blood glucose excursion (MAGE) values taken within 2 days of admission. Patients with higher GV (highest MAGE tertile) were compared with those with lower GV (first and second MAGE tertiles).

Results. – A total of 204 patients were included: median age was 72 (61–81) years; 32% were female; HbA_{1c} was 7.3% (6.4–8.2%); diabetes duration was 10 (2–17.5) years; and MAGE value was 0.65 (0.43–0.92) g/L. Compared with those with lower GV, patients with the highest GV were more often women, treated with previous insulin, and had higher blood glucose and HbA_{1c} levels. In addition, patients with elevated GV had significantly higher SYNTAX scores: 17 (10–28) vs. 12 (6–22) ($P = 0.009$). Indeed, SYNTAX scores (OR: 1.05, 95% CI: 1.02–1.08; $P = 0.001$) remained independently associated with high GV beyond HbA_{1c} levels (OR: 1.51, 95% CI: 1.2–1.89; $P < 0.001$).

Conclusion. – In AMI patients with poorly controlled diabetes, GV is associated with CAD severity beyond chronic hyperglycaemia. Although no causality can be determined from our observational study, the results suggest that, in AMI, early evaluation of GV might contribute to the identification of those diabetes patients at high risk, and serve as a therapeutic target for both primary and secondary prevention.

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in diabetes patients, 40% of whom also have coronary artery disease (CAD) whereas 15% have congestive heart failure [1]. In particular, CVD in type 2 diabetes (T2D) arises on average 14.6 years earlier, and is also more severe and diffuse, than in non-diabetic subjects. In fact, hyperglycaemia exacerbates the mechanisms underlying atherosclerosis and heart failure. At present, reducing CV risk in diabetes patients is a multifactorial strategy that includes statins and/or other lipid-lowering agents, antihypertensive therapies and hyperglycaemic control.

The relationship between chronic hyperglycaemia and CVD in patients with T2D has been well documented in many epidemiological studies, including the United Kingdom Prospective Diabetes Study (UKPDS) [2] and European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) [3], and confirmed in a large meta-analysis [4] which showed that every 1% increase in HbA_{1c} is associated with an 18% greater risk for CVD. Although short-term glycaemic-control trials have not shown any reduction of CAD [5,6], a decrease in CV risk secondary to

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diminution of hyperglycaemia has been clearly demonstrated in long-term glycaemic-control trials such as the UKPDS [7] and Veterans Affairs Diabetes Trial (VADT) [8], and a meta-analysis [9].

However, chronic hyperglycaemia may not be the only factor promoting CVD in patients with T2D, as glycaemic variability (GV) is also suspected to be involved. In acute myocardial infarction (AMI), high GV, as assessed by mean amplitude of glycaemic excursion (MAGE) values, is associated with a poor prognosis at 1 year even after adjusting for Global Registry of Acute Coronary Events (GRACE) scores [10]. Moreover, in 88 non-diabetic patients with AMI, MAGE values were found to be an independent factor for progression of angiographic coronary lesions over an 11-month follow-up period [11]. Yet, as these studies were performed in only a limited number of patients who were either non-diabetic or had well-controlled diabetes, the association between GV and CAD has never been addressed in patients with severe diabetic disease, in whom chronic hyperglycaemia might overcome the effect of GV on CAD.

Thus, the present prospective study of poorly controlled T2D patients admitted to hospital for AMI aimed to evaluate GV to determine the potential factors associated with high GV, and address the association of GV and extent of coronary artery lesions on coronary angiography.

Patients and methods

Study population

This prospective study included consecutive patients hospitalized within 48 h of symptom onset in the intensive cardiology care unit of Dijon University Hospital who underwent coronary angiography for AMI between 1 March 2015 and 28 February 2017. Inclusion criteria were documented T2D (with or without insulin therapy before admission) treated by continuous rapid-acting intravenous insulin (CRIVI) within the first 48 h because of admission blood glucose levels > 180 mg/dL, as recommended [12], and with at least 10 capillary blood glucose samples taken within 48 h of admission. Patients without CRIVI or < 10 capillary blood glucose samples were excluded from the study (Fig. 1).

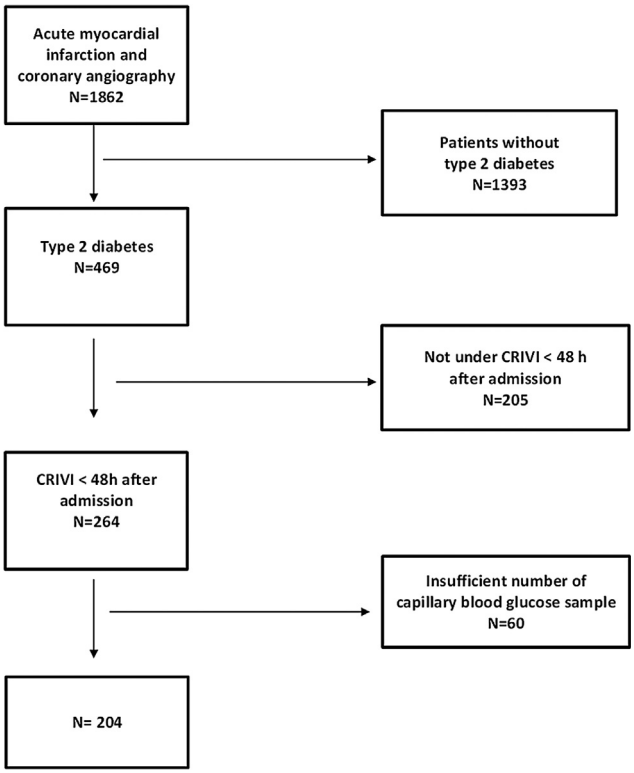

Fig. 1. Flow chart of study population selection. CRIVI: continuous rapid-acting intravenous insulin.

Data collection

CVD risk factors of interest included age, gender, hypertension, diabetes, obesity [body mass index (BMI) > 30 kg/m^2], treated hypercholesterolaemia or total cholesterol > 2.5 g/L, familial history of CAD (premature CAD in at least one first-degree relative aged < 55 years for men or < 65 years for women) and current smoking. A history of CV was also collected [CAD, carotid atheroma, chronic kidney disease (CKD)], while systolic (SBP) and diastolic blood pressure (DBP) and heart rate were taken on admission, as were also blood samples for glucose, glycated haemoglobin (Hb) A_{1c}, lipid parameters, C-reactive protein (CRP) and serum creatinine levels. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Troponin Ic peak was derived from three blood samples taken every 8 h within 24 h of admission, and left ventricular ejection fraction (LVEF) was measured within 24 h of admission by an experienced practitioner using Simpson's biplane method of disks [13].

The SYNTAX Score, which characterizes coronary artery lesion severity (length, bifurcation, extended disease, calcifications, thrombus, total occlusion), was calculated first [before percutaneous coronary intervention (PCI)] and then followed by a residual SYNTAX score (after PCI) [14]. Lesions were considered complex if they caused ≥ 50% stenosis and had two or more of the following morphological features:

- ulceration (sacciform extraluminal opacification);
- irregularities or crenellated edges;
- sharp stenotic wall angulation; and;
- endoluminal defects compatible with thrombus.

The GRACE score, which assesses a patient's individual risk for in-hospital and 6-month mortality, was also assessed [15].

Continuous rapid-acting intravenous insulin protocol and glycaemic control

The implementation of CRIVI was initiated when blood glucose at admission was ≥ 180 mg/dL (10.0 mmol/L) and/or preprandial glucose was ≥ 140 mg/dL (7.77 mmol/L) and perfused throughout the intensive care unit stay. All other chronic treatments for diabetes (such as oral antidiabetic medications or insulin) were discontinued during this period. The target glycaemic range was 140–180 mg/dL (7.7–10 mmol/L). Capillary blood glucose monitoring was done 1 h after initiation of insulin therapy and every 2 h thereafter, before and 2 h after every meal, and in the evening at bedtime. Dosages were adjusted according to the current French guidelines [16].

Glucose variability as the average of glycaemic excursions

GV was measured by MAGE, which was established to account for peak and nadir blood glucose levels beyond mean blood glucose values over the course of a day, according to the following formula [17]:

where λ is the peak-to-nadir difference, x is the number of valid observations and y is the standard deviation (SD) of the average capillary glycaemia test results.

The objective of the MAGE formula is to consider only major changes in blood glucose levels. Therefore, only variations greater

than the SD of the mean blood glucose value during the observation period are taken into consideration. The MAGE is considered the gold standard for assessment of GV, particularly in studies based on continuous or discontinuous glucose monitoring; its value is independent of the mean blood glucose, but reflects the instability of daily blood glucose levels in diabetes patients. Mean glucose (mGlucose) concentration was calculated over two consecutive days by intensive glucose monitoring (10-point glycaemic profile). In addition, as MAGE is positively correlated with HbA_{1c} levels, a metric such as the coefficient of variation (CV) for glucose as an index of short-term variability not dependent on overall exposure to glucose, was also computed [18]. Glucose CV [(SD/mGlucose)/100] was calculated by averaging all daily values over the sampling period (48 h) and expressed as a percentage (%).

Statistical analysis

Given the lack of any available reference or standard value, GV was analyzed as tertiles: the first two tertiles were considered low GV, while the last tertile was considered high. Patients were also divided according to their initial SYNTAX scores: the first and second tertiles comprised the low SYNTAX group, whereas patients in the third tertile constituted the high SYNTAX group.

Dichotomous variables were expressed as n (%) and continuous variables as mean ± SD, with normality of variables determined by the Kolmogorov–Smirnov test. For categorical data, chi-squared or Fisher's exact test was used, with comparisons of continuous data done by Student's t test for normal variables or the Mann–Whitney test for non-Gaussian variables. The significance threshold was set at 5%. Backward multivariate logistic regression models were constructed using either variables predictive of high GV or high SYNTAX Scores in univariate analyses, with an inclusion and exclusion threshold set at 5%. These analyses were all performed with IBM SPSS version 22 software (IBM Corp., Armonk, NY, USA).

Results

Of the 1862 patients hospitalized for AMI, 469 patients (25%) had T2D (with or without insulin treatment). However, 205 of them were excluded because they had not been given the CRIVI protocol at admission, and 60 lacked enough capillary blood glucose measurements to calculate their MAGE values (Fig. 1). The final study population (n = 204) had a mean age of 72 ± 12 years, 32% were female and 82% had hypertension (Table 1).

Characteristics and determinants of high GV

Compared with patients with low GV, those in the high GV group were two times more frequently female. On admission, they had higher heart rates, but lower DBP. There was also a trend towards increased rates of kidney failure and high GRACE Risk Scores in the high GV group (Table 1). In addition, high GV patients were more frequently being treated with insulin prior to admission, and more often had elevated levels of blood glucose and HbA_{1c}. Glucose CV had a median value of 24.18 ± 11.34%, and was markedly more elevated (+80%) in the high *vs* low GV patients. Diabetes duration, however, was similar in both groups.

As for coronary angiography data (Table 2), rates of PCI were similar in the two groups. However, initial SYNTAX scores of patients in the high GV group were 40% higher than those in the low GV group [17 (10–28) vs. 12 (6–22), respectively; P = 0.009], and the residual SYNTAX Score was as much as four times higher [8 (0–15) vs. 2 (0–6), respectively; P = 0.002]. Furthermore, more lesions were reported in patients with high GV (3.4 ± 2.0 vs. 2.8 ± 1.9, respectively; P = 0.035) and, although there was a trend towards a greater number of complex lesions, the difference was not significant (P = 0.112). In-hospital mortality was also similar in both groups.

Logistic regression analysis showed that the initial SYNTAX Score was associated with higher GV on univariate analysis, along with female gender, chronic or acute diabetes-related parameters (diabetes duration, previous insulin therapy, HbA_{1c}, blood glucose at admission) and eGFR. In fact, the initial SYNTAX Score (OR: 1.05, 95% CI: 1.02–1.08) remained strongly associated with high GV even after adjustments for confounding factors (Table 3).

Characteristics and determinants of high SYNTAX Score

Patient's characteristics, clinical and biological data on admission, and hospital complications according to CAD extent (SYNTAX score tertiles) are presented in Table 4. Patients with the highest SYNTAX Scores were 6 years older, smoked less, more often had a history of stroke or transient ischaemic attacks (TIAs), and were twice as likely to also have CKD. Of the diabetes-related parameters, the MAGE and CV for glucose showed trends towards higher values in the high SYNTAX Score group (Table 4) and across SYNTAX tertiles (Fig. 2). In contrast, chronic blood glucose control and mean glucose values were similar in both groups (P = 0.425 and P = 0.159, respectively). Patients in the highest SYNTAX tertile also had higher GRACE Scores and lower LVEF rates ($P < 0.001$). Albeit not significant, a slightly increased rate of hospital deaths was found in the high-risk group (P = 0.061). Multivariate logistic regression analysis showed that high GV (OR: 2.08, 95% CI: 1.11–3.92) was an independent predictor of severity of CAD beyond age and previous stroke/TIAs (Table 5). When the CV for glucose was tested as a covariate instead of GV in multivariate analysis, the CV also tended to be associated with SYNTAX Score (P = 0.053). These findings further support the hypothesis of an association between short-term GV and coronary atheroma burden.

Discussion

Only a few studies have suggested that GV might be associated with severity of CAD. In fact, whether GV has an impact on CAD even in patients with poorly controlled T2D, where chronic hyperglycaemia could eclipse the effect of GV on CAD extent, remains to be demonstrated. Nevertheless, to the best of our knowledge, our present findings reveal for the first time that GV is associated with CAD severity in patients with uncontrolled T2D and goes beyond HbA_{1c} levels. Moreover, these data support the hypothesis of a pathophysiological link between GV and coronary lesions, which could be at least partly independent of chronic hyperglycaemia.

Prediction of glycaemic variability in coronary artery disease patients

Very few studies have addressed daily GV in AMI patients. One recent pilot study tested continuous glucose monitoring in 48 patients with stable CAD (43% with diabetes) scheduled to undergo PCI [19]. The authors highlighted a significant relationship between MAGE and postprocedural creatinine and troponin evolution, and also identified three independent factors associated with changes in post-PCI renal function:

- age;
- impaired left ventricular (LV) function; and;
- high GV within 24 h post-PCI.

In cases of type 2 myocardial infarction (11%), only high GV within 24 h post-PCI was an independent factor. In addition, the

Table 1
Study population characteristics according to glycaemic variability (GV).

	Total population (n = 204)	Low GV group (n = 136)	High GV group (n = 68)	P[a]
Cardiovascular (CV) risk factors				
Age, years	72 (61–81)	71 (61–81)	75 (61–81)	0.510
Female gender	65 (32)	32 (24)	33 (49)	[b]
Hypertension	165 (82)	107 (79)	58 (87)	0.206
Smokers	36 (18)	28 (21)	8 (12)	0.119
Body mass index, kg/m^2	28 (26–32)	29 (26–33)	28 (25–32)	0.433
Hypercholesterolaemia	127 (63)	85 (63)	42 (64)	0.926
Familial history of CAD	45 (23)	30 (23)	15 (23)	0.978
CV history				
CAD	62 (30)	41 (30)	21 (31)	0.914
Carotid atheroma	10 (5)	8 (6)	2 (3)	0.501
Stroke/TIAs	18 (9)	12 (9)	6 (9)	1
Chronic kidney disease	27 (13)	14 (10)	13 (19)	0.080
Diabetes characteristics				
Insulin	54 (27)	31 (23)	23 (34)	0.092
Oral antidiabetic medication	144 (671)	100 (74)	44 (65)	0.192
Diabetes duration, years	10.0 (2.0–17.5)	9.0 (2.0–16.0)	10.0 (3.0–21.3)	0.171
MAGE	0.65 (0.43–0.92)	0.51 (0.36–0.65)	1.05 (0.91–1.27)	[b]
HbA_{1c}, %	7.3 (6.4–8.2)	7.0 (6.3–8.1)	7.7 (6.6–8.7)	[c]
Admission glucose, mmol/L	10.07 (7.79–14.06)	9.59 (7.21–13.10)	11.96 (9.10–16.10)	[c]
Mean glucose, mmol/L	8.64 (7.43–10.62)	8.09 (7.04–9.96)	9.79 (8.42–11.72)	[b]
Coefficient of variation, %[e]	24.18 ± 11.34	19.28 ± 7.64	34.00 ± 11.20	[b]
Clinical characteristics				
STEMI	101 (50)	71 (52)	30 (44)	0.276
GRACE Score	156 ± 40	152 ± 40	163 ± 38	0.071
LVEF, %	55 (40–60)	55 (45–60)	50 (40–60)	0.248
Heart rate, bpm	82 ± 19	80 ± 19	86 ± 19	[d]
Systolic BP, mmHg	143 ± 30	145 ± 29	138 ± 32	0.157
Diastolic BP, mmHg	80 ± 19	82 ± 18	76 ± 20	[d]
Biological data				
Total cholesterol, mg/dL	173 (143–209)	173 (142–210)	173 (145–211)	0.622
LDL cholesterol, mg/dL	97 (69–133)	97 (70–130)	98 (66–138)	0.810
HDL cholesterol, mg/dL	42 (35–50)	42 (35–50)	42 (35–52)	0.253
Triglycerides, mg/dL	136 (99–213)	139 (103–218)	126 (87–193)	0.253
Troponin Ic peak, µg/L	14.0 (2.85–68.8)	13.5 (2.6–78.0)	16.0 (3.2–65.8)	0.971
eGFR, mL/min/1.73 m^2	74.2 (48.2–82.4)	76.8 (51.0–93.8)	67.9 (44.9–90.9)	0.109
CRP > 3 mg/L	142 (71)	91 (67)	51 (77)	0.149
Hospital outcome				
Death	19 (9.3)	11 (8.1)	8 (11.8)	0.394

Data are presented as n (%), mean ± SD or median (interquartile range).
BP: blood pressure; CAD: coronary artery disease; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL/LDL: high-density/low-density lipoprotein; LVEF: left ventricular ejection fraction; MAGE: mean amplitude of glycaemic excursion; STEMI: ST-segment elevation myocardial infarction; TIAs: transient ischaemic attacks.
[a] High GV (last tertile) vs. low GV (first and second tertiles).
[b] $P < 0.001$.
[c] $P < 0.01$.
[d] $P < 0.05$.
[e] for glucose.

Table 2
Angiography data according to glycaemic variability (GV).

	Total population (n = 204)	Low GV group (n = 136)	High GV group (n = 68)	P[a]
SYNTAX Score				
Initial (pre-PCI)	14 (7–24)	12 (6–22)	17 (10–28)	[b]
Residual (post-PCI)	2 (0–8)	2 (0–6)	8 (0–15)	[b]
Coronary lesions				
Number of lesions	3.0 ± 2.0	2.8 ± 1.9	3.4 ± 2.0	[c]
Number of complex lesions	2.1 ± 1.8	1.9 ± 1.8	2.4 ± 1.9	0.112
PCI	154 (76)	101 (74)	53 (78)	0.565

Data are presented as n (%), mean ± SD or median (interquartile range).
PCI: percutaneous coronary intervention.
[a] High GV (last tertile) vs. low GV (first and second tertiles).
[b] $P < 0.01$.
[c] $P < 0.05$.

Table 3
Logistic regression analysis for factors associated with higher glycaemic variability (GV).

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Female (vs. male) gender	3.064	1.650–7.68	[a]	4.146	2.052–8.377	[a]
Initial SYNTAX score, per unit	1.034	1.009–1.058	[b]	1.046	1.017–1.076	[a]
HbA_{1c}, per %	1.428	1.156–1.764	[a]	1.506	1.202–1.888	[a]
Admission blood glucose, per mmol/L	1.120	1.052–1.193	[a]	–	–	–
Duration of diabetes, per years	1.033	0.998–1.070	0.069	–	–	–
Insulin (vs. no insulin) therapy	1.731	0.911–3.292	0.094	–	–	–
eGFR, per unit	0.990	0.980–1.001	0.077	–	–	–

eGFR: estimated glomerular filtration rate.
[a] $P < 0.001$.
[b] $P < 0.01$.

Table 4
Population characteristics at admission according to SYNTAX score (last vs. first and second tertiles).

	Lower SYNTAX scores (n = 136)	Higher SYNTAX scores (n = 68)	P
Cardiovascular (CV) risk factors			
Age (years)	71 (59–79)	76 (67–82)	[b]
Female gender	48 (35)	17 (25)	0.137
Hypertension	115 (85)	50 (76)	0.129
Smokers	30 (22)	6 (9)	0.019
Body mass index, kg/m^2	29 (26–33)	28 (25–31)	0.057
Hypercholesterolaemia	90 (66)	37 (57)	0.203
Family history of CAD	27 (21)	18 (29)	0.229
CV history			
CAD	40 (29)	22 (32)	0.667
Carotid atheroma	7 (5)	3 (4)	0.819
Stroke/TIAs	7 (5)	11 (16)	[b]
Chronic kidney disease	13 (10)	14 (21)	[c]
Diabetes characteristics			
Insulin	32 (24)	22(32)	0.178
Oral diabetes treatment	101(74)	43(63)	0.103
Diabetes duration, years	9.0 (2.0–17.3)	10.0 (3.0–18.0)	0.594
Admission glucose, mmol/L	9.65 (7.59–13.91)	11.30 (8.13–15.10)	0.116
MAGE	0.63 (0.40–0.82)	0.69 (0.44–1.08)	0.075
Last tertile of MAGE	38 (28)	30 (44)	[c]
HbA_{1c}, %	7.2 (6.3–8.2)	7.3 (6.5–8.6)	0.425
Mean glucose, mmol/L	8.36 (7.37–10.45)	8.91 (7.81–11.44)	0.159
Coefficient of variation, %[d]	23.50 ± 10.47	25.55 ± 12.88	0.224
Clinical characteristics			
STEMI	70 (51)	31(46)	0.428
Non-STEMI	66 (49)	37 (54)	0.428
GRACE Score	147.8 ± 40.3	171.8 ± 32.6	[a]
LVEF, %	55 (45–60)	45 (35–55)	[a]
Heart rate, bpm	79 ± 18	86 ± 21	[c]
Systolic BP, mmHg	143 ± 32	142 ± 28	0.732
Diastolic BP, mmHg	81 ± 20	78 ± 17	0.380
Biological data			
Total cholesterol, mg/dL	174 (146–209)	167 (139–216)	0.501
LDL cholesterol, mg/dL	98 (69–130)	95 (69–142)	0.983
HDL cholesterol, mg/dL	42 (35–50)	42 (36–50)	0.778
Triglycerides, mg/dL	153 (108–236)	116 (85–169)	[b]
Troponin Ic peak, µg/L	12 (2–66)	17 (4–83)	0.204
eGFR, mL/min/1.73 m^2	76.4 (53.4–93.5)	68.4 (40.2–86.5)	[c]
CRP > 3 mg/L	88 (65)	54 (82)	[c]
Hospital outcome			
Death	9 (6.6)	10 (14.7)	0.061

Data are presented as n (%), mean ± SD or median (interquartile range).
BP: blood pressure; CAD: coronary artery disease; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL/LDL: high-density/low-density lipoprotein; LVEF: left ventricular ejection fraction; MAGE: mean amplitude of glycaemic excursion; STEMI: ST-segment elevation myocardial infarction; TIAs: transient ischaemic attacks.
[a] $P < 0.001$.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] For glucose.

authors found no correlation with HbA_{1c} levels [19], thereby suggesting that myocardial lesions might be primarily influenced by hypoglycaemia and rapid spikes in blood glucose, whereas renal lesions might be more sensitive to slower and longer hyperglycaemic excursions [19].

Our present work also addressed predictive factors for early levels of GV in diabetes patients with AMI undergoing IV insulin therapy. The results have revealed that elevated HbA_{1c} values are associated with glycaemic instability in the acute phase of MI, which is in agreement with findings in postoperative patients [20]. In 120 patients who underwent on-pump coronary artery bypass graft (CABG) surgery, diabetes and high HbA_{1c} (> 7%) values were predictive of high GV [20].

Glycaemic variability and coronary artery disease extent

An association between high GV and SYNTAX scores (reflecting the CAD burden in diabetes with AMI) has thus far not been reported. In a small group of patients with CAD and diabetes, a significant relationship on linear regression analysis between GV assessed by MAGE values and CAD severity was previously reported [21]. However, the study addressed patients with a recent history of diabetes (5 years) and stable CAD. Furthermore, the rate of those using insulin therapy, a major determinant of glycaemic control, was unknown, as no information was available on antidiabetic treatments. In contrast, our present study population included long-standing diabetes patients (> 10 years) years) with advanced CAD and hyperglycaemia requiring insulin therapy.

In T2D, carotid intima–media thickness, as a surrogate marker of atheroma burden, is significantly correlated with at-home postprandial hyperglycaemic peaks independently of HbA_{1c} levels [22]. In 286 newly diagnosed diabetes patients with no history of CVD who underwent PCI [23], MAGE ($P < 0.001$) was an independent predictor of angiographic CAD severity beyond age ($P < 0.001$), HbA_{1c} ($P = 0.022$) and high-sensitivity CRP (hs-CRP; $P = 0.005$). GV has previously been characterized in ST-elevation myocardial infarction (STEMI) patients fitted with a glycaemic Holter monitor for 72 h: those in the highest GV tertile more frequently had diabetes and multivessel disease than those in the

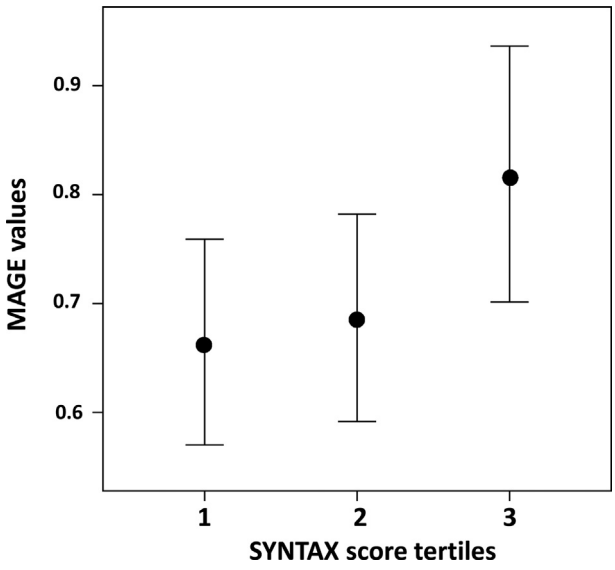

Fig. 2. Mean amplitude of blood glucose excursion (MAGE) values according to tertile of SYNTAX scores (P = 0.154).

lower tertiles [53% vs. 14% ($P < 0.001$) and 81% vs. 66% (P = 0.037), respectively] [24]. Also, subgroup analyses in patients with diabetes showed a gradual increase in rates of the primary endpoint (CV death, recurrent MI, unstable angina, culprit lesion revascularization) across tertiles (8%, 25% and 40%; P = 0.038) at 30 days. Moreover, the number and complexity of lesions and non-culprit vessel revascularization were higher (15%, 21% and 32%, respectively; P = 0.032). Intravascular ultrasound (IVUS) analysis of a small series of AMI patients not receiving insulin therapy showed that higher GV was significantly associated with a larger plaque burden in culprit vessels and an increased lipid but decreased fibrous content consistent with higher coronary plaque instability [25]. These GV associations with coronary plaque vulnerability parameters were independent of the conventional glycaemic indicators [HbA_{1c}, homoeostasis model assessment of insulin resistance (HOMA-IR), fasting plasma glucose].

Another index of plaque vulnerability has been provided by optical coherence tomography (OCT)-guided analysis of non-culprit coronary arteries of 46 acute coronary syndrome (ACS) patients: those with the highest MAGE values more frequently had diabetes (37% *vs* 16%) and thinner fibrous cap thicknesses, and a greater prevalence of thin-cap fibroatheroma at non-culprit plaques in non-culprit vessels. Furthermore, MAGE, in addition to hs-CRP, was found to be an independent predictor of rapid progression of non-culprit lesions after ACS [11].

Whether this relationship translates to altering the prognosis was recently suggested by observational and experimental studies. After MI, higher admission GV was a stronger predictor of 1-year MACE (CV death, reinfarction, revascularization of culprit lesion) than admission glucose and previous long-term abnormal glycometabolic status, even after adjusting for GRACE scores (OR: 2.41, 95% CI: 1.27–9.10; P = 0.017) [10]. More severe adverse LV remodelling associated with variations in glucose levels has been shown on magnetic resonance imaging (MRI) in both preclinical and human prospective studies [26,27]. Indeed, negative correlations between glycaemic instability and the myocardial salvage index on cardiac MRI 7 days after STEMI were found in both diabetes and non-diabetes groups [28].

The underlying pathophysiological mechanisms to explain the link between wide variations in glucose blood levels and CAD severity have yet to be explored. Fluctuating blood glucose levels may have a negative influence on the CV system through multiple pathways: GV could induce proinflammatory cytokine release [interleukin (IL)-6, IL-8, IL-18 and tumour necrosis factor (TNF)-α] and a decrease in nitric oxide bioavailability and, subsequently, endothelial dysfunction [29–32]. The latter is predictive of a future CVD event and an early player in the development of CV complications in both T2D and type 1 diabetes (T1D). Acute fluctuations in glycaemia can lead to profound modifications of vascular homoeostasis, including endothelial dysfunction through increased production of reactive oxygen species (ROS), and be more damaging than stable constant high blood glucose [29]. Also, there is a positive correlation between postprandial glucose fluctuations and urinary isoprostanes strongly suggestive of increased oxidative stress; this relationship was observed across all HbA_{1c} levels, thereby highlighting the targeted effect of transient hyperglycaemic excursions on oxidative stress [29]. Interventional studies of antidiabetic agents, such as glucagon-like peptide (GLP)-1 agonists, to minimize glycaemic excursions and reduce oxidative stress could address part of this issue.

Study limitations

The present study has several limitations. MAGE assessment was limited to capillary glycaemia (10-point calculations), with no continuous glucose monitoring (CGM). As CGM is based on continuous glucose management over prolonged periods of time, it provides a more comprehensive and precise record of GV than glucose profiling based on serial samples at 10 points over 48 h. Also, as CGM covers the entire day/night period, it is considered the reference method for assessment of short-term GV. However, a 10-point discontinuous glucose profile of capillary glycaemia can be routinely obtained in the current clinical practice for the management of AMI in diabetes, as the GV calculation is made by averaging the 10-point values over two consecutive days. In fact, the Kroc Collaborative Study Group showed that the seven-point MAGE calculation strongly correlated with the 22-point

Table 5
Logistic regression analysis for factors associated with higher initial SYNTAX Scores.

	Univariate			Multivariate 1			Multivariate 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age, per years	1.039	1.011–1.067	[a]	1.039	1.011–1.068	[a]	1.037	1.009–1.066	[a]
History of stroke/TIAs (vs. no history)	3.556	1.311–9.644	[b]	3.810	1.360–10.677	[b]	3.681	1.321–10.255	[b]
Higher GV (last vs. first tertiles)	2.036	1.109–3.739	[b]	2.084	1.108–3.921	[b]	–	–	–
Chronic kidney disease (*vs* no disease)	2.453	1.080–5.569	[b]	–	–	–	–	–	–
Triglycerides, per unit	0.672	0.482–0.935	[b]	–	–	–	–	–	–
CV for glucose, per %	1.016	0.990–1.042	0.225				–	–	–
Glucose CV > 36% (vs. ≤ 36%)	2.466	1.112–5.470	[b]				2.248	0.989–5.107	0.053

TIAs: transient ischaemic attacks; GV: glycaemic variability; CV: coefficient of variation.
[a] $P < 0.01$.
[b] $P < 0.05$.

glycaemic calculation ($P = 0.001$) [33]. In addition, given the observational nature of our study, it was not possible to demonstrate a causal relationship between CAD burden and GV levels. Therefore, our findings can only suggest an association, but not causality. Finally, SYNTAX Scores were not obtained for the entire study population (only 183/196 patients, or 94%), as some patients did not undergo PCI, thereby diminishing the statistical power of the analysis.

Conclusion

Several pieces of evidence have raised the possibility that GV could be contributing to the development of diabetes complications, including macrovascular disease. Our results show an association between GV and an index of the extent of coronary artery lesions in patients with T2D and AMI, thereby suggesting that oscillating blood glucose may override consistently high glucose levels in influencing CV diabetes complications. Thus, further studies are now needed to specifically address this issue.

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Disclosure of interest

The authors declare that they have no competing interest.

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